Makuch Marcin, Makuch Marcelina, Krzewicka-Romaniuk Ewa, Dzida Grzegorz. Sodium-glucose co-transporter 2 inhibitors – a review article. Journal of Education, Health and Sport. 2019;9(9):42-49. eISSN 2391-8306. DOI http://dx.doi.org/10.5281/zenodo.3372353
http://ojs.ukw.edu.pl/index.php/johs/article/view/7297

The journal has had 7 points in Ministry of Science and Higher Education parametric evaluation. Part B item 1223 (26/01/2017).
1223 Journal of Education, Health and Sport eISSN 2391-8306 7

The authors declare that there is no conflict of interests regarding the publication of this paper.

Received: 05.08.2019. Revised: 15.08.2019. Accepted: 20.08.2019.

Sodium-glucose co-transporter 2 inhibitors – a review article

Marcin Makuch[1], Marcelina Makuch[2], Ewa Krzewicka-Romaniuk[3], Grzegorz Dzida[1]

[1] Chair and Department of Internal Medicine, Medical University of Lublin, Poland
[2] Chair and Department of Pneumonology, Oncology and Allergology, Medical University of Lublin, Poland
[3] Department of Pathophysiology, Medical University of Lublin, Poland

Corresponding author:
Marcin Makuch,
ul. Staszica 16,
20-081 Lublin, Poland,
e- mail: marcinm45@gmail.com

Abstract:

Antihyperglycemic interventions have centered on increasing insulin availability, improving insulin sensitivity or restoring β-cell activity to normalize plasma glucose levels in patients with type 2 diabetes mellitus. An alternative strategy is to enhance urinary glucose excretion by targeting renal sodium-glucose co-transporters (SGLTs). Sodium-glucose co-transporter 2 (SGLT2) inhibitors reduce blood glucose by increasing urinary glucose excretion and present a valuable therapeutic option for the treatment of type 2 diabetes. Presently, clinically available SGLT2 inhibitors include canagliflozin, dapagliflozin and empagliflozin [1, 2].

Keywords: sodium-glucose co-transporter 2 inhibitors, glucose, type 2 diabetes, cardiovascular effects

1. Sodium-glucose co-transporter 2 inhibitors - mechanism of action

Glucose, which is a polar compound, cannot penetrate through the walls of the nephron which are made of lipids. Consequently, glucose is reabsorbed by the nephrons with help of glucose transporters which utilize ATP and generate an ionic gradient that helps in the transport of glucose. Described glucose transporters are present in the proximal convoluted tubule (PCT) of the nephron. The apical membrane of the PCT contains of two types of Na^+/K^+ co-transporters: SGLT1 and SGLT2. SGLT2 reabsorb of approximately 90% of the filtered glucose load whereas SGLT1 is responsible for the remaining 10% (Figure 1). Therefore, SGLT2 are an ideal target for the treatment of diabetes.

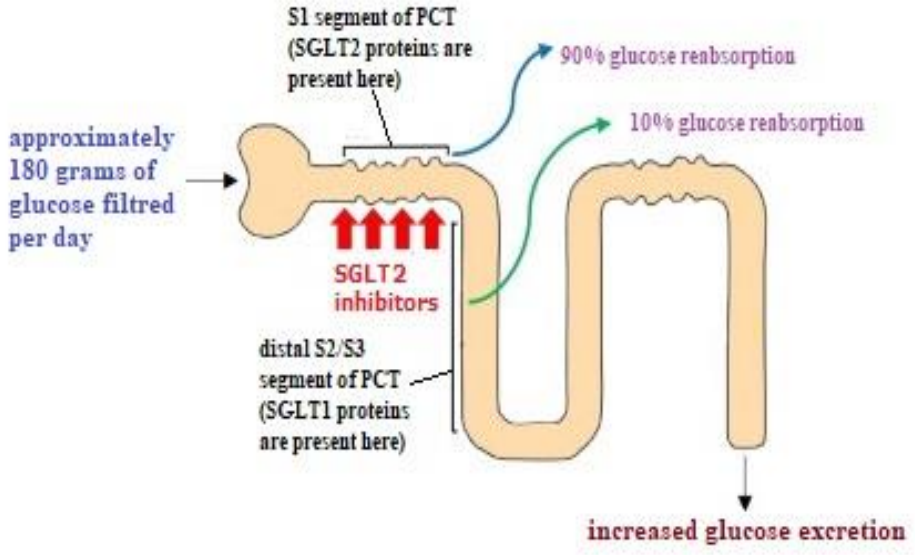

Figure 1 – Mechanism of action of SGLT2 inhibitors

The active transport of glucose is carried out by SGLT through the Na^+/K^+ATPase channel (present in the basolateral membrane of the PCT): the Na^+/K^+ ATPase pump expels out 3 Na^+ ions from the lumen into the blood and in return brings in 2 K^+ ions. This leads to formation of a downhill Na^+ ion gradient. The SGLT proteins employ the energy generated by this downhill gradient to transport 1 glucose molecule and 1 Na^+ ion across the apical membrane of the PCT. The glucose is then extruded into the blood with the help of facilitated transport by glucose transporter type 2 (GLUT2) and glucose transporter type 1 (GLUT1), which are present on the basolateral membrane of the PCT.

SGLT2 lower blood glucose and glycated hemoglobin (A1C) levels but this effect is limited due to the filtered load of glucose and the osmotic diuresis. The glucose-lowering effect is independent of insulin – that is why SGLT2 inhibitors usually do not cause hypoglycaemia [3, 4, 5].

2. Indications

The majority of patients with type 2 diabetes does not demand SGLT2 inhibitors as initial therapy. Most patients should be firstly treated with diet, weight reduction, exercise and metformin. However, SGLT2 inhibitors might be useful option in:

- obese and hypertensive patients (because of potential weight loss and antihypertensive benefits)
- patients with overt cardiovascular disease (eg heart failure) not reaching glycemic goals with metformin and lifestyle modifications
- patients with nephropathy (urine albumin-to-creatinine >300 mg/g and estimated glomerular filtration rate (eGFR) <90 mL/min/1.73m^2)
- as a second agent in patients with inadequate control on metformin who are unable to consider injection therapy
- patients who are at high risk of hypoglycemia (the risk of hypoglycemia with SGLT2 inhibitors is small when compared to insulin and sulfonylureas)
- as a third-line agent in patients with inadequate glycemic control on two oral agents (eg, metformin and sulfonylurea) if for some reason combination metformin and insulin is not a therapeutic option
- as a third-line agent in patients not adequately controlled on metformin and insulin therapy, in whom glucagon-like peptide-1 (GLP-1) receptor agonists are contraindicated and increasing insulin dosing would lead to weight gain
- treatment of diabetic nephropathy - SGLT2 inhibitors reduce the risk of kidney disease progression and cardiovascular disease in patients with type 2 diabetes with nephropathy (estimated or measured urine albumin excretion >300 mg per day) and an estimated GFR (eGFR) ≥30 mL/min per 1.73 m^2 [6, 7].

3. Contraindications

Patients with predisposition for bacterial urinary tract infections or genitourinary yeast infections should be warned of increased risk while using SGLT2 inhibitors. These agents are also contraindicated for patients with:

- type 1 diabetes
- type 2 diabetes and renal insufficiency (GFR < 45 mL/min/1.73m^2)
- ketosis-prone type 2 diabetes [8].

4. Drug interaction

SGLT2 inhibitors may cause a mild degree of dehydration. Therefore, they should not be used with other drugs predisposing to acute renal injury (nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, diuretics, contrast agents, mannitol, calcineurin inhibitors). For this reason, it seems reasonable to discontinue SGLT2 inhibitors before performing any diagnostic imaging with contrast agents.

What is more, SGLT2 inhibitors should be used with caution if the patient has comorbidities that might predispose to acute renal injury (hypovolemia, heart failure, liver injury, renal artery stenosis). As a consequence, patients should be clinically evaluated before starting SGLT2 inhibitors therapy - volume status, renal function (serum creatinine with eGFR) and liver function should be assessed [9].

5. Clinical outcomes

SGLT2 inhibitors have a unique mechanism of action. Not only, do they bring out the hypoglycemic effect and weight reduction, but also reduce blood pressure thanks to diuretic and natriuretic effect. The benefits from using SGLT2 inhibitors are following:

- **glycemic efficacy** — SGLT2 inhibitors are relatively weak glucose-lowering agents, with mean reductions in A1C compared with placebo ranging between 0,4 to 1,1 percentage depending on baseline level of hyperglycemia;

- **cardiovascular effects** — empagliflozin and canagliflozin appear to decrease mortality in patients with type 2 diabetes and overt cardiovascular disease (CVD); dapagliflozin does not appear to reduce atherosclerotic cardiovascular morbidity or cardiovascular mortality, but similar to empagliflozin and canagliflozin, dapagliflozin reduces hospitalization for heart failure
- **microvascular outcomes** — there are a number of trials evaluating microvascular outcomes in patients taking SGLT2 inhibitors: in a meta-analysis of the 3 major CVD outcome trials, empagliflozin, canagliflozin and dapagliflozin reduced progression of nephropathy, with a similar effect observed in patients with established atherosclerotic CVD or multiple risk factors for CVD
- **weight loss** — SGLT2 inhibitors decrease weight: in 12-week trials of dapagliflozin, canagliflozin, and empagliflozin, weight loss of 2 to 3 kg was reported and the weight loss appears to be sustained over time; however, due to the osmotic and possibly diuretic effect of flozins it is important to differentiate between a weight reduction because of fluid loss and that due to fat loss [10, 11, 12, 13, 14, 15, 16].

6. Adverse effects of SGLT2 inhibitors

The most common side effects caused by SGLT2 inhibitors include fungal infections of the external genitourinary organs and urinary tract infections. In addition, especially among the elderly patients with impaired renal function, who take diuretics, SGLT2 inhibitors may cause symptomatic hypotension.

Adverse effects of SGLT2 inhibitors are following:

- **infections of genitourinary tract** – increased incidence of vulvovaginal candidiasis, urinary tract infections and potentially fatal urosepsis, pyelonephritis and necrotizing fasciitis of the perineum (Fournier's gangrene), related to the induction of glucosuria (which supports the growth of fungi or other organisms and promotes more frequent genitourinary infections)
- **bladder cancer** – especially among dapagliflozin users (it can be associated with increased surveillance of patients treated for genitourinary infections)
- **hypotension** — SGLT2 inhibitors cause an osmotic diuresis and intravascular volume contraction; therefore in older patients taking diuretics, angiotensin-converting enzyme (ACE) inhibitors, or angiotensin receptor blockers (ARBs), SGLT2 inhibitors may cause symptomatic hypotension
- **acute kidney injury** – in patients taking canagliflozin or dapagliflozin, but probably other risk factors occurred (eg, depleted volume, hypotension, or taking other medications that could affect the kidneys)
- **bone fractures** — a possible mechanism, particularly for fractures occurring in older individuals after only 12 weeks of therapy, is orthostatic hypotension resulting in postural dizziness and falls, but also SGLT2 inhibitors may adversely affect bone density
- **diabetic ketoacidosis** — that is why serum ketones should be obtained in any patient with nausea, vomiting, or malaise while taking SGLT2 inhibitors, and SGLT2 inhibitors should be discontinued if acidosis is confirmed
- **amputations** — compared with some oral and injectable diabetes agents, SGLT2 inhibitors are associated with an increased risk of amputation; as a consequence, patients taking SGLT2 inhibitors should be monitored for signs and symptoms of foot ulceration (so called diabetic foot) [17, 18, 19, 20].

7. Drug information

Empagliflozin, canagliflozin and dapagliflozin are representatives of SGLT2 inhibitors used in clinical practice. Soon, ertugliflozin will be also available.

a) Empagliflozin

- dosing: the initial dose is 10 mg daily, and it can be increased to 25 mg once daily (as tolerated to achieve glycemic goals), empagliflozin is taken orally once daily in the morning with or without food
- should not be initiated in patients with eGFR <45 mL/min/1.73 m^2
- may be used in patients with hepatic impairment.
- indications: treatment of type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycemic control; risk reduction of cardiovascular mortality in adults with type 2 diabetes mellitus and established cardiovascular disease
- contraindications: history of serious hypersensitivity to empagliflozin or any component of the formulation; severe renal impairment (eGFR <30 mL/minute/1.73 m^2), end-stage renal disease or dialysis
- adverse reactions: genitourinary fungal infection, urinary tract infections, increased urine output, dyslipidemia, increased thirst, nausea, increased haematocrit, hypotension (due to intravascular volume depletion), bone fractures; risk of intravascular volume depletion, renal impairment may be increased in elderly patients
- monitoring parameters: blood glucose, HbA_{1c},renal function, volume status (eg, blood pressure, hematocrit, electrolytes); LDL-C; if signs/symptoms of ketoacidosis (eg, nausea/vomiting, abdominal pain, malaise, shortness of breath), confirm diagnosis by direct measurement of blood ketones and arterial pH [21]

b) Canagliflozin

- dosing: the initial dose is 100 mg once daily, and it can be increased to 300 mg daily to achieve glycemic goals, canagliflozin is taken orally before the first meal of the day
- eGFR ≥30 to <45 mL/minute/1.73 m^2: Use not recommended for initiation of therapy or when eGFR is persistently <45 mL/minute/1.73 m^2.
- indications: treatment of type 2 diabetes mellitus (noninsulin dependent, NIDDM) as an adjunct to diet and exercise to improve glycemic control; risk reduction of major cardiovascular events (cardiovascular death, nonfatal MI, and nonfatal stroke) in adults with type 2 diabetes mellitus and established cardiovascular disease
- contraindications: history of serious hypersensitivity to canagliflozin or any component of the formulation; severe renal impairment (eGFR <30 mL/minute/1.73 m^2); end-stage renal disease or patients on dialysis
- adverse reactions: increased serum potassium, genitourinary fungal infection, urinary tract infection, increased urine output, renal insufficiency, falling, fatigue, hypoglycemia, hypovolemia, increased thirst, abdominal pain, constipation, nausea, increased haemoglobin, hypersensitivity reactions, bone fractures, hypotension, ketoacidosis, lipid abnormalities, lower limb amputation
- monitoring parameters: blood glucose, HbA_{1c}, renal function, volume status (eg, blood pressure, hematocrit, electrolytes); serum potassium, serum magnesium and phosphate, LDL-C, hypersensitivity reactions, lower limb and feet (sores, ulcers, infection); if signs/symptoms of ketoacidosis (eg, nausea/vomiting, abdominal pain, malaise, shortness of breath), confirm diagnosis by direct measurement of blood ketones and arterial pH [22]

c) Dapagliflozin

- dosing: 10 mg once daily can be taken any time of day with or without food

- if eGFR ≥45 mL/minute/1.73 m^2: no dosage adjustment necessary, but if eGFR 30 to <45 mL/minute/1.73 m^2: the use is not recommend, however, recommendations regarding indicated level of eGFR for initiation or continued use may vary in other regions
- indications: **a**s an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
- contraindications: history of serious hypersensitivity to dapagliflozin or any component of the formulation; severe renal impairment (eGFR <30 mL/minute/1.73 m^2), end-stage renal disease (ESRD), or patients on dialysis
- adverse reactions: urinary tract infections, genitourinary fungal infection, increased urine output, influenza dyslipidemia, nausea, hyperphosphatemia, nasopharyngitis, hypovolemia, renal insufficiency, back pain, limb pain, bone fractures, hypotension, ketoacidosis, lipid abnormalities, necrotizing fasciitis, bladder cancer, renal or hepatic impairment
- monitoring parameters: blood glucose, HbA_{1c}, renal function, LDL-C, volume status (eg, blood pressure, hematocrit, electrolytes); if signs/symptoms of ketoacidosis (eg, nausea/vomiting, abdominal pain, malaise, shortness of breath), confirm diagnosis by direct measurement of blood ketones and arterial pH [23]

d) Ertugliflozin

- dosing: the initial dose is 5 mg once daily and may be increased to a maximum dose of 15 mg once daily to achieve glycemic goals, ertugliflozin is taken once daily in the morning with or without food
- if eGFR 30 to <60 mL/minute/1.73 m^2: Not recommended for initiation of therapy in preexisting impairment or continued use when eGFR is persistently within this range during therapy
- indications: as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
- contraindications: history of serious hypersensitivity reaction to ertugliflozin or any component of the formulation; severe renal impairment, end-stage renal disease, or dialysis
- adverse reactions: genitourinary fungal infection, headache, hypovolemia, hypoglycaemia, increased thirst, weight loss, increased urine output, vulvovaginal pruritus, back pain, nasopharyngitis, renal insufficiency, hypersensitivity reactions, bone fractures, hypotension, ketoacidosis, lipid abnormalities, lower limb amputation
- monitoring parameters: blood glucose, HbA_{1c}, renal function, volume status (eg, blood pressure, hematocrit, electrolytes), phosphate, LDL-C, genital mycotic infections and urinary tract infection, hypersensitivity reactions, lower limb and feet (sores, ulcers, infection); if signs/symptoms of ketoacidosis confirm diagnosis by direct measurement of blood ketones and arterial pH [24].

8. Choice of therapy

SGLT2 inhibitors are administered to individuals with type 2 diabetes who had previously reported poorly controlled blood glucose. They are effective in: reducing HbA1c, improving weight loss in conjunction with advice on lifestyle and diet, lowering systolic blood pressure and decreasing FPG levels. When a decision has been made to use an SGLT2 inhibitor, empagliflozin, canagliflozin, dapagliflozin, and ertugliflozin are available options.

If a patient with type 2 diabetes has a prior history of myocardial infarction or stroke, empagliflozin is suggested rather than another SGLT2 inhibitor. Although canagliflozin also shows cardiovascular benefits, there is an increase in the risk of lower limb amputations and fractures in canagliflozin-treated patients that was not observed in trials of empagliflozin

or dapagliflozin. There are no trials directly comparing the individual SGLT2 inhibitors, but in network meta-analyses canagliflozin 300 mg reduced A1C to a slightly greater extent than dapagliflozin 10 mg or empagliflozin 25 mg (mean difference -0.2 percentage points) [25, 26].

References:

1. Dzida G, Pacjent z cukrzycą; In: Problemy okołooperacyjne u osób w wieku podeszłym. Pod red. nauk. Tomasza Grodzickiego, Jakub Keniga, Warszawa 2018, PZWL Wydawnictwo Lekarskie; 133-140, bibliogr, 978-83-200-5601-3.
2. Pasterczyk K, Mulawka P, Gajda P, Kuzemko-Baranowska D, Dzida G, Flozins 2018 - the landscape after EMPA-REG OUTCOME, Chor. Serca i Naczyń 2018;15;3,159–164.
3. Clar C, Gill JA, Court R, Waugh N. Systematic review of SGLT2 receptor inhibitors in dual or triple therapy in type 2 diabetes. BMJ Open 2012; 2.
4. Musso G, Gambino R, Cassader M, Pagano G. A novel approach to control hyperglycemia in type 2 diabetes: sodium glucose co-transport (SGLT) inhibitors: systematic review and meta-analysis of randomized trials. Ann Med 2012; 44:375.
5. American Diabetes Association. Pharmacologic approaches to glycemic treatment. Standards of medical care in diabetes -2017. Diabetes Care. 2017; 40 (Suppl 1): S64–S74
6. Palmer SC, Mavridis D, Nicolucci A, et al. Comparison of Clinical Outcomes and Adverse Events Associated With Glucose-Lowering Drugs in Patients With Type 2 Diabetes: A Meta-analysis. JAMA 2016; 316:313.
7. Zaccardi F, Webb DR, Htike ZZ, et al. Efficacy and safety of sodium-glucose co-transporter-2 inhibitors in type 2 diabetes mellitus: systematic review and network meta-analysis. Diabetes Obes Metab 2016; 18:783.
8. Musso G, Gambino R, Cassader M, Pagano G. A novel approach to control hyperglycemia in type 2 diabetes: sodium glucose co-transport (SGLT) inhibitors: systematic review and meta-analysis of randomized trials. Ann Med 2012; 44:375.
9. Shyangdan DS, Uthman OA, Waugh N. SGLT-2 receptor inhibitors for treating patients with type 2 diabetes mellitus: a systematic review and network meta-analysis. BMJ Open 2016; 6:e009417.
10. Pratley RE, Eldor R, Raji A, et al. Ertugliflozin plus sitagliptin versus either individual agent over 52 weeks in patients with type 2 diabetes mellitus inadequately controlled with metformin: The VERTIS FACTORIAL randomized trial. Diabetes Obes Metab 2018; 20:1111.
11. Rosenstock J, Jelaska A, Frappin G, et al. Improved glucose control with weight loss, lower insulin doses, and no increased hypoglycemia with empagliflozin added to titrated multiple daily injections of insulin in obese inadequately controlled type 2 diabetes. Diabetes Care 2014; 37:1815.
12. Rosenstock J, Frias J, Páll D, et al. Effect of ertugliflozin on glucose control, body weight, blood pressure and bone density in type 2 diabetes mellitus inadequately controlled on metformin monotherapy (VERTIS MET). Diabetes Obes Metab 2018; 20:520.
13. Vasilakou D, Karagiannis T, Athanasiadou E, et al. Sodium-glucose cotransporter 2 inhibitors for type 2 diabetes: a systematic review and meta-analysis. Ann Intern Med 2013; 159:262.
14. Liu XY, Zhang N, Chen R, et al. Efficacy and safety of sodium-glucose cotransporter 2 inhibitors in type 2 diabetes: a meta-analysis of randomized controlled trials for 1 to 2years. J Diabetes Complications 2015; 29:1295.
15. Zelniker TA, Wiviott SD, Raz I, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet 2019; 393:31.

16. Zelniker TA, Wiviott SD, Raz I, et al. Comparison of the Effects of Glucagon-Like Peptide Receptor Agonists and Sodium-Glucose Cotransporter 2 Inhibitors for Prevention of Major Adverse Cardiovascular and Renal Outcomes in Type 2 Diabetes Mellitus. Circulation 2019; 139:2022.
17. Nyirjesy P, Zhao Y, Ways K, Usiskin K. Evaluation of vulvovaginal symptoms and Candida colonization in women with type 2 diabetes mellitus treated with canagliflozin, a sodium glucose co-transporter 2 inhibitor. Curr Med Res Opin 2012; 28:1173.
18. Kumar S, Costello AJ, Colman PG. Fournier's gangrene in a man on empagliflozin for treatment of Type 2 diabetes. Diabet Med 2017; 34:1646.
19. Ueda P, Svanström H, Melbye M, et al. Sodium glucose cotransporter 2 inhibitors and risk of serious adverse events: nationwide register based cohort study. BMJ 2018; 363:k4365.
20. Weir MR, Januszewicz A, Gilbert RE, et al. Effect of canagliflozin on blood pressure and adverse events related to osmotic diuresis and reduced intravascular volume in patients with type 2 diabetes mellitus. J Clin Hypertens (Greenwich) 2014; 16:875.
21. Jardiance (empagliflozin) [prescribing information]. Ridgefield, CT: Boehringer Ingelhei m Pharmaceuticals, Inc; June 2019.
22. Invokana (canagliflozin) [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals; June 2019.
23. Farxiga (dapagliflozin) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; June 2019.
24. Steglatro (ertugliflozin) (prescribing information). Whitehouse Station, NJ: Merck Sharp & Dohme Corp; June 2019.
25. Neal B, Perkovic V, Matthews DR, et al. Rationale, design and baseline characteristics of the CANagliflozin cardioVascular Assessment Study-Renal (CANVAS-R): A randomized, placebo-controlled trial. Diabetes Obes Metab 2017; 19:387.
26. Bersoff-Matcha SJ, Chamberlain C, Cao C, et al. Fournier Gangrene Associated With Sodium-Glucose Cotransporter-2 Inhibitors: A Review of Spontaneous Postmarketing Cases. Ann Intern Med 2019.